Stiffness at shear-wave elastography and patient presentation predicts upgrade at surgery following an ultrasound-guided core biopsy diagnosis of ductal carcinoma in situ

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Introduction

Breast lesions yielding an image guided biopsy diagnosis of Ductal Carcinoma in Situ (DCIS) may contain invasive foci when the entire lesion is removed at surgery. Such an upgrade may lead to further surgery, especially to the axilla (1). Predicting the likelihood of upgrade to invasion is useful as it may change options for initial surgery, particularly with regard to sentinel node biopsy. Factors predicting upgrade of DCIS lesions diagnosed with stereotactic biopsy have been well established in the literature and include mammographic extent, palpability and grade of DCIS diagnosed on percutaneous biopsy (2-4). However, factors predicting upgrade following an US guided biopsy of DCIS have not been well established and only two previous studies have studied shear wave elastography (SWE) in this context (5-8). A number of reports of SWE of the breast have shown that DCIS lesions are less stiff than invasive cancers (9, 10). These findings suggest that SWE may be useful in predicting the presence of invasion. The aim of this study is to establish the role of mammographic, ultrasound, SWE and other pre-operative features in predicting invasion at surgical excision in lesions yielding an US guided 14g core biopsy diagnosis of DCIS.

Methods

SWE has been part of the routine breast ultrasound examination at our centre since November 2009. Quantitative data are routinely extracted prospectively within a few days of the examination and before biopsy results were known. In accordance with the applicable National Research Ethics Service guidance, ethical approval for this retrospective study of prospectively acquired anonymised data was not required (National Research Ethics Service, 2008(11)). However, written informed consent to use images was obtained, according to routine practice.

All patients with US visible lesions were scanned using the Aixplorer ultrasound system (SuperSonic Imagine^{TM}, Aix en Provence, France) between December 2010 and December 2015 Those patients with lesions visible on greyscale US and subjected to ultrasound guided 14g needle core biopsy yielding a biopsy diagnosis of DCIS were included in this study. Patients with biopsies from elsewhere in the ipsilateral breast showing invasive disease were excluded.

All patients were scanned and biopsied with ultrasound guidance by one of five breast radiologists or an advanced radiography practitioner trained to perform and interpret breast ultrasound. These practitioners had between 7 and 22 years of breast ultrasound experience and had at least 3 months experience of performing SWE of solid breast lesions prior to the commencement of the study. Greyscale and SWE images were obtained during the standard ultrasound appointment. Four SWE images in two orthogonal planes were obtained. The region of interest (ROI) utilised in all cases was 2mm in diameter. A threshold value of 50 kilopascals (kPa) was used for mean elasticity (Emean) to dichotomise the elasticity data. This threshold has been validated in previous studies using SWE to differentiate between benign and malignant masses (12, 13). The average of the 4 values from the 4 images was used for analysis. Additionally the mean SWE value across the entire study group was also used as a possible cut off value.

The size and BIRADS classification of the greyscale US abnormalities were recorded as was the presence or absence of an US visible mass or calcification (some lesions were visible as textural change with or without US visible calcifications). The dominant mammographic feature was also recorded as was the BIRADS classification of any mammographic abnormality.

The source of the patient from either mammographic screening or the symptomatic referral service was noted as was the palpability of the lesion. The histological grade of DCIS present on the US guided 14g core biopsy was recorded. Regarding subsequent surgical excisions, micro-invasion was included in the DCIS group as such lesions do not routinely warrant an axillary nodal procedure. The size, grade, vascular invasion and nodal status of any invasive foci were collected from the surgical pathology report.

The significance of differences between groups was established using the chi-square test with $p < 0.05$ taken to indicate statistically significant differences.

Results

Analysis of 1954 US visible masses with histological correlation yielded 57(3%) patients with an US 14g core biopsy diagnosis of DCIS who had subsequent surgical excision. The mean age of the patients was 60 yrs (range 23 -82 yrs). 33(58%) lesions were screen-detected while 24(42%) resulted from investigation of symptoms. At surgical excision 24(42%) patients had invasive foci while 33 had DCIS only. The features of the 24 invasive cancers are shown in Table 1. 12 of 24 (50%) invasive foci were less than 10mm in diameter and 2 of 24 (8%) were node positive. The mean histological whole tumour size (i.e. extent including DCIS) was 28mm for the pure DCIS lesions and 53 mm for those containing an invasive focus.

The relationship between pre-operative factors and presence of invasion are shown in Tables 2 to 4. Patients presenting with symptoms were more likely to have invasive foci than patients presenting through screening (58% [14 of 24] vs. 30% [10 of 33], p=0.03). Patients whose lesions had a mean stiffness at SWE of > 50kPa were more likely to have an invasive focus then women with lesions whose mean stiffness was <50kPa (51% [20 of 39] vs. 22% [4 of 18], p=0.04). The mean stiffness value in the entire study group was 84kPa. Using this as a cut off value did not aid the identification of those women with invasive foci. The mean stiffness values for women with and without invasion were 89 kPa and 78kPa respectively, while the median values were 74 kPa and 56 kPa. Trends towards younger women and women with high greyscale US suspicion scores (BI-RADS) did not achieve statistical significance.

Patient age, core biopsy DCIS grade, US lesion size (mean size was 17mm), mammographic features and mammography BI-RADS score showed no significant relationship with the presence of invasion at excision. The presence of an ultrasound visible mass or calcification likewise did not have an association with invasion. Palpability of the lesion did not have a statistically significant relationship with invasion as 10 of 18 (55%) of palpable lesions were invasive compared to 14 of 39(36%) impalpable lesions (p=0.16).

Combining the two significant predictors of invasion further improves risk stratification (Table 5) with symptomatic and stiff lesions having a risk of invasion of 67% (12 of 18) while soft lesions presenting at screening had only a 17% (2 of 12) risk of invasion (p=0.02).

Discussion

We have shown that the stiffness of lesions yielding a core biopsy diagnosis of DCIS has a significant relationship with the risk of occult invasion at excision. We have also found that occult invasion is commoner in women whose lesions are symptomatic compared to women presenting through mammographic screening. The combination of these two factors allows a high risk group of women with stiff lesions that are symptomatic to be identified. This group has a risk of invasion of 67% and it contains half the women in the study group with invasion. Thus, this is a group where sentinel lymph node biopsy (SNB) may be justified or, alternatively, another approach such as re-biopsing these women using a large volume vacuum-assisted biopsy (VAB) technique to try and confirm the presence of invasion could be considered. Women whose lesions are not symptomatic or stiff have a low risk of invasion (17%) and neither repeat biopsy nor SNB would seem justified. The two intermediate groups (screen detected and stiff, or symptomatic but soft) also have a relatively low risk of invasion and SNB or further biopsy is probably not required in these patients either. It should also be noted that the nodal positivity rate in those women with invasion in this study was very low (8%).

A number of previous studies have shown that invasive cancers tend to be stiffer than DCIS lesions (9, 10) while two previous studies have shown that stiffness is associated with upgrade following an ultrasound guided biopsy with a DCIS diagnosis (5,8). Neither of these studies combined the significant factors to provide the risk stratification shown in table 5 which may aid clinical management.

What is unclear is whether the increased stiffness in the upgrade group is because the invasive focus itself was imaged but not biopsied or whether increased stiffness identifies DCIS lesions at particular risk of invasion. The stiffness of invasive cancers is usually most marked at the lesional/stromal boundary and is thought to be due in part, to the stiffness of the extracellular matrix (ECM) produced by cancer associated fibroblasts (CAFs). CAFs are important in tumour progression, invasion and metastasis (14-

16) and this is likely to be the reason why stiffness at SWE has been shown to be an independent predictor of nodal metastasis (17). Similarly the stiffness detected in DCIS lesions is likely to be due to the stiffness of the extracellular matrix produced by CAFs, which are also present within DCIS lesions. Stromal influences are known to be important in initiating invasion within DCIS lesions (14-16). It is therefore possible that the increased stiffness seen with DCIS lesions with occult invasion is due to stiff stroma produced by activated CAFs which also initiate invasion, in contrast to less stiff stroma in DCIS lesions with lower invasive potential.

We have also found that occult invasion is commoner in women whose lesions were symptomatic compared to women presenting through mammographic screening. It has been noted in previous studies that palpability is associated with upgrade following a biopsy diagnosis of DCIS (2-4). Not all patients with symptoms have a palpable lesion (some may have presented with nipple discharge) and some screen detected lesions are palpable. We found palpability less predictive than the source of referral.

A number of previous studies have studied the greyscale US features of lesions yielding an US guided core biopsy diagnosis of DCIS and upgrade to invasive cancer. The results of these studies have been inconsistent. Some have found abnormal axillary lymph nodes and large lesion size to be associated with higher rates of upgrade to invasive cancer (6, 7). In our study, we did not find US lesion size a useful predictor of invasion. We did not assess the value of abnormal axillary lymph nodes in our study as the node positivity rate was so low.

Studies looking at upgrade following stereotactic biopsy of malignant calcifications have found that DCIS grade of the biopsy and calcification extent are predictors of occult invasion (2-4). Neither of these factors was significant in the present study. The reason why grade of DCIS does not predict invasion in

the current study is not clear. There is not a hint of a difference so the small numbers in the current study does not appear to be the reason for this finding.

There are a number of limitations in the current study. The study was carried out in a single centre and has a relatively small numbers of patients. The centre has a special interest in SWE so whether the results are generalizable is open to question. However the results are consistent with the two other study examining the role of SWE in predicting invasion after an US guided core biopsy result of DCIS (5,8).

In conclusion, we have found that stiffness on SWE and the referral source of the patient are predictors of occult invasion in women with an US guided core biopsy diagnosis of DCIS and that the combination of these factors allows stratification of invasion risk which might be used to guide future patient management.

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